

Ignatius J. Turchi*, Cynthia A. Maryanoff and Antonietta R. Mastrocola

Research and Development Division, Smith Kline and French Laboratories,
Philadelphia, Pennsylvania 19101

Received June 9, 1980

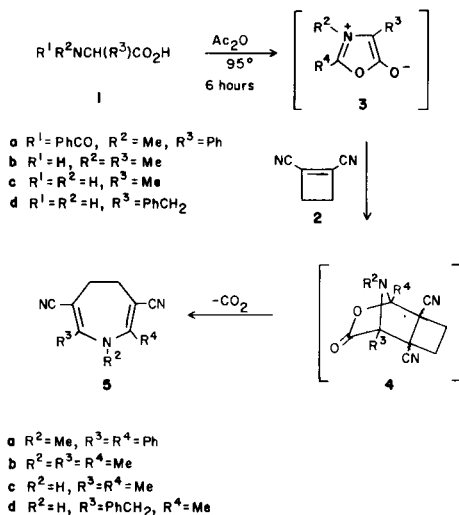
Heating primary or secondary α -amino acids in acetic anhydride in the presence of 1,2-dicyanocyclobutene leads to 4,5-dihydroazepines *via* the intermediacy of mesoionic oxazolium 5-oxides.

J. Heterocyclic Chem., 17, 1593 (1980).

Mesoionic compounds are versatile intermediates in heterocyclic synthesis (2). Over the past decade, oxazolium 5-oxides, otherwise known as Munchnones, have been exploited extensively in pyrrole synthesis (2-4). 1,3-Dipolar cycloaddition of the masked azomethine ylide of the Munchnone system to various acetylenic dipolarophiles followed by a 1,3-dipolar cycloreversion of carbon dioxide from the initially-formed adduct provides pyrrole derivatives (4a). Hershenson (5) and Albonico, *et al.* (6), among others (7) have applied this concept successfully to the synthesis of the indolizidine and pyrrolizidine skeletons *via* the use of Munchnones derived from cyclic α -amino acids such as proline and piperidinecarboxylic acid. Rebek and Gehret have explored this pathway in an approach to mitosenes (8).

Several groups have studied the 1,3-dipolar cycloaddition of mesoionic oxazoles and thiazoles to cyclopropenes and cyclopropanones (9). This process leads to the formation of pyridine derivatives. 1,4-Thiazine 1,1-dioxides arise from the dipolar addition of 2,3-diphenylthiirene 1,1-dioxide to mesoionic oxazoles (10). 2,4-Diphenyl-3-methyloxazolium 5-oxide reacts with cyclobutenes to afford monocyclic 4,5-dihydroazepines (11).

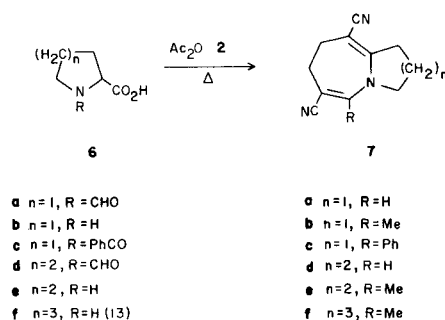
Scheme I



We have found 1,2-dicyanocyclobutene (2) (12) to be an effective dipolarophile in its reactions with a variety of Munchnones to provide both monocyclic and fused bicyclic 4,5-dihydroazepines **5** and **7**, respectively, in good yield. As depicted in Scheme I below, this transformation probably involves initial formation of the mesoionic oxazoles of type **3** from the α -amino acids **1**, followed by 1,3-dipolar cycloaddition of **2** to **3**. Elimination of carbon dioxide with cleavage of the cyclobutane ring of **4** leads to the observed 4,5-dihydroazepines **5**. Support for this mechanism comes from the case of **1a** in which the mesoionic oxazole **3a** was isolated (4a) and converted to **5a** by warming with **2** in toluene.

In a similar manner, the fused bicyclic dihydroazepines **7** are formed in good yields when the cyclic α -amino acids **6** are heated in acetic anhydride in the presence of **2** (Scheme II).

Scheme II



Thus the procedure outlined above constitutes a viable method for the construction of the 1-azabicyclo[5.n.0]-alkane system (14). We are currently investigating the reactions of mesoionic systems with cyclobutenes and heterocyclobutenes in order to extend the scope of this transformation to include other types of 7-membered ring heterocycles.

EXPERIMENTAL

Melting points were recorded with a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 283 Spectrophotometer, nmr with a Perkin-Elmer

R32 (90 MHz) spectrometer, and mass spectra with either a Hitachi RMU 6E (electron impact) or a Finnigan GC/MS Model 3200 (chemical ionization) mass spectrometer at 70 eV. Combustion analyses for C, H, and N were performed by our Analytical/Physical Chemistry Department.

1-Methyl-2,7-diphenylazepine-3,6-dicarbonitrile (5a).

A mixture of 2,4-diphenyl-3-methyloxazolium 5-oxide (3a, 10 mmoles, 2.51 g.) (4a) and 1,2-dicyanocyclobutene (2, 12 mmoles, 1.25 g.) in toluene (20 ml.) was heated to 50° in a water bath for 30 minutes. The mixture was concentrated under reduced pressure and the residue recrystallized from ethanol to give 5a (85%, 2.65 g.).

General Procedure for the Preparation of 5a,d and 7a-f.

A mixture of the amino acid 1 or 6 (10 mmoles) and 1,2-dicyanocyclobutene (2, 12 mmoles) in acetic anhydride (10 ml.) was heated (95°, 6 hours for 5a-d; reaction temperatures and times for 7a-f, given below). The volatile materials were removed under reduced pressure and the residue was dissolved in methylene chloride, washed with 10% sodium bicarbonate solution, then with water and dried (magnesium sulfate) and the solvent removed under reduced pressure. The residue was passed through a column of silica gel (chloroform eluent) and the material thus obtained was recrystallized (solvents given below) to afford analytically pure products.

1-Methyl-2,7-diphenylazepine-3,6-dicarbonitrile (5a).

This compound was recrystallized from ethanol, 78% yield, m.p. 243-245°; ir (potassium bromide): 770, 1335, 1345, 1575, 1585, 1625, 2205, 2215, 2940, 3065 cm⁻¹; nmr (DMSO-d₆): δ 2.36 (s, 3H), 2.81 (s, 4H), 7.48 (s, 10H); me: (electron impact) m/e 311 (M⁺), 283, 118.

Anal. Calcd. for C₂₁H₁₃N₃: C, 81.00; H, 5.50; N, 13.49. Found: C, 81.03; H, 5.49; N, 13.42.

1,2,7-Trimethylazepine-3,6-dicarbonitrile (5b).

This compound was recrystallized from aqueous ethanol, 93% yield, m.p. 93-94°; ir (potassium bromide): 1000, 1050, 1110, 1130, 1160, 1180, 1220, 1260, 1330, 1395, 1480, 1580, 1640, 2200, 2850 cm⁻¹; nmr (deuteriochloroform): δ 2.21 (s, 6H), 2.52 (s, 4H), 3.00 (s, 3H); ms: (electron impact) m/e 187 (M⁺), 159, 56, 43.

Anal. Calcd. for C₁₁H₁₃N₃: C, 70.57; H, 7.00; N, 22.44. Found: C, 71.01; H, 6.98; N, 22.34.

2,7-Dimethylazepine-3,6-dicarbonitrile (5c).

This compound was recrystallized from aqueous ethanol, 76% yield, m.p. 185-186°; ir (potassium bromide): 1040, 1220, 1300, 1390, 1420, 1540, 1620, 1680, 2200, 2970, 3100, 3180, 3300, 3350 cm⁻¹; nmr (deuteriochloroform): δ 2.00 (s, 6H), 2.37 (s, 4H), 6.87 (br s, 1H, NH); ms: (electron impact) 173 (M⁺), 70, 43.

Anal. Calcd. for C₁₀H₁₁N₃: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.73; H, 6.46; N, 24.10.

2-Benzyl-7-methylazepine-3,6-dicarbonitrile (5d).

This compound was recrystallized from aqueous ethanol, 84% yield, m.p. 115-116°; ir (potassium bromide): 695, 1300, 1400, 1440, 1500, 1540, 1635, 1680, 2200, 2950, 3100, 3190, 3300, 3350, cm⁻¹; nmr (deuteriochloroform): δ 2.02 (s, 3H), 2.50 (s, 4H), 3.73 (s, 2H), 6.83 (br s, 1H, NH), 7.27 (s, 5H); ms: (chemical ionization) m/e 250 (M⁺ + 1), 249 (M⁺).

Anal. Calcd. for C₁₆H₁₅N₃: C, 77.08; H, 6.06; N, 16.85. Found: C, 77.23; H, 5.76; N, 16.73.

2,3,7,8-Tetrahydro-1H-pyrrolo[1,2-a]azepine-6,9-dicarbonitrile (7a).

This compound was recrystallized from aqueous ethanol, 52% yield, m.p. 138-139° (reaction time-temperature: 12 hours 95°); ir (potassium bromide): 1310, 1400, 1425, 1600, 1650, 2190, 2970 cm⁻¹; nmr (deuteriochloroform): δ 2.01 (m, 2H), 2.55 (s, 4H), 2.92 (t, J = 8 Hz, 2H), 3.79 (t, J = 7.5 Hz, 2H), 6.74 (s, 1H); ms: (electron impact) m/e 185 (M⁺), 157, 133.

Anal. Calcd. for C₁₁H₁₁N₃: C, 71.33; H, 5.99; N, 22.68. Found: C, 71.33; H, 5.88; N, 22.63.

2,3,7,8-Tetrahydro-5-methyl-1H-pyrrolo[1,2-a]azepine-6,9-dicarbonitrile (7b).

This compound was recrystallized from ethanol, 85% yield, m.p. 117-118° (reaction time-temperature: 6 hours 90°); ir (potassium bromide): 1195, 1225, 1305, 1355, 1385, 1585, 1625, 2150, 2180, 2940 cm⁻¹; nmr (deuteriochloroform): δ 1.98 (m, 2H), 2.26 (s, 3H), 2.53 (s, 4H), 2.92 (t, J = 8.0 Hz, 2H), 3.80 (t, J = 7.5 Hz, 2H); ms: (electron impact) 199 (M⁺), 184, 171, 147.

Anal. Calcd. for C₁₂H₁₃N₃: C, 72.34; H, 6.58; N, 21.08. Found: C, 72.26; H, 6.92; N, 21.08.

2,3,7,8-Tetrahydro-5-phenyl-1H-pyrrolo[1,2-a]azepine-6,9-dicarbonitrile (7c).

This compound was recrystallized from aqueous ethanol or toluene-hexane, 65% yield, m.p. 136-137° (reaction time-temperature: 12 hours 95°); ir (potassium bromide): 695, 745, 1155, 1185, 1225, 1310, 1385, 1585, 1620, 2185, 2900, 3050 cm⁻¹; nmr (deuteriochloroform): δ 1.79 (m, 2H), 2.60 (br s, 4H), 2.91 (t, J = 8.0 Hz, 2H), 3.25 (t, J = 8.0 Hz, 2H), 7.38 (br s, 5H); ms: (electron impact) 261 (M⁺), 233, 209, 104.

Anal. Calcd. for C₁₇H₁₅N₃: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.01; H, 5.70; N, 16.09.

1,2,3,4,8,9-Hexahydropyrrolo[1,2-a]azepine-7,10-dicarbonitrile (7d).

This compound was recrystallized from ethanol, 50% yield, m.p. 124-126° (reaction time-temperature: 2 hours 75°); ir (potassium bromide): 1165, 1205, 1330, 1405, 1445, 1465, 1590, 1645, 2195, 2875, 2965 cm⁻¹; nmr (deuteriochloroform): δ 1.80 (m, 4H), 2.53 (s) and 2.65 (m, overlapping signals, 6H), 3.48 (distorted t, 2H), 6.59 (s, 1H); ms: (electron impact) m/e 199 (M⁺), 171, 147, 82.

Anal. Calcd. for C₁₂H₁₃N₃: C, 72.33; H, 6.57; N, 21.09. Found: C, 72.30; H, 6.55; N, 21.18.

1,2,3,4,8,9-Hexahydro-6-methylpyrido[1,2-a]azepine-7,10-dicarbonitrile (7e).

This compound was recrystallized from aqueous ethanol, 85% yield, m.p. 95-96° (reaction time-temperature 2 hours 85°); ir (potassium bromide): 1310, 1330, 1405, 1455, 1580, 1630, 2200, 2260, 2900-3000 cm⁻¹; nmr (deuteriochloroform): δ 1.82 (m, 4H), 2.23 (s, 3H), 2.55 (s, 4H), 2.76 (m, 2H), 3.42 (distorted t, 2H); ms: (chemical ionization) m/e 214 (M⁺ + 1).

Anal. Calcd. for C₁₃H₁₃N₃: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.30; H, 6.96; N, 19.82.

2,3,4,5,9,10-Hexahydro-7-methyl-1H-azepino[1,2-a]azepine-8,11-dicarbonitrile (7f).

This compound was recrystallized from ethanol, 73% yield, m.p. 124-126° (reaction time-temperature: 4 hours, 85°); ir (potassium bromide): 975, 1190, 1215, 1230, 1250, 1265, 1315, 1325, 1415, 1445, 1570, 1640, 2180, 2860, 2920 cm⁻¹; nmr (deuteriochloroform): δ 1.70 (br s, 6H), 2.25 (s, 3H), 2.55 (s, 4H), 2.70 (m, 2H), 3.50 (distorted t, 2H); ms: (chemical ionization) m/e 228 (M⁺ + 1).

Anal. Calcd. for C₁₆H₁₇N₃: C, 73.98; H, 7.54; N, 18.48. Found: C, 73.83; H, 7.60; N, 18.79.

Acknowledgement.

The authors thank the members of our Analytical/Physical Chemistry Department for the spectra and combustion analyses.

REFERENCES AND NOTES

- (1a) This paper is dedicated to Professor Rolf Huisgen on the occasion of his sixtieth birthday; (b) Presented at the Third IUPAC Symposium on Organic Synthesis, June 15-20, 1980, Madison, Wisconsin.
- (2a) W. D. Ollis and C. A. Ramsden, *Adv. Heterocyclic Chem.*, **19**, 1 (1976); (b) M. Ohta and H. Kato, in "Nonbenzenoid Aromatics", Vol. 1, J. P. Snyder, Ed., Academic Press, New York, N.Y., 1969, p. 117.

- (3) I. J. Turchi and M. J. S. Dewar, *Chem. Rev.*, **75**, 389 (1975).
- (4a) R. Huisgen, H. Gotthardt, H. O. Bayer and F. C. Schafer, *Chem. Ber.*, **103**, 2611 (1970); (b) W. E. McEwen, A. V. Grossi, R. J. MacDonald and A. P. Stamegna, *J. Org. Chem.*, **45**, 1301 (1980); (c) J. A. Myers, L. D. Moore, W. L. Whitter, S. L. Council, R. M. Waldo, J. L. Lanier and B. U. Omoji, *ibid.*, **45**, 1202 (1980).
- (5) F. M. Hershenson, *J. Heterocyclic Chem.*, **16**, 1093 (1979), and references cited therein.
- (6a) I. A. Benages and S. M. Albonico, *J. Org. Chem.*, **43**, 4273 (1978); (b) M. T. Pizzorno and S. M. Albonico, *ibid.*, **39**, 731 (1974).
- (7a) W. K. Anderson and P. F. Corey, *J. Org. Chem.*, **42**, 559 (1977); (b) T. Uchida, S. Tsubokawa, K. Harihara and K. Matsumoto, *J. Heterocyclic Chem.*, **15**, 1303 (1978).
- (8) J. Rebek and J.-C. E. Gehret, *Tetrahedron Letters*, 3027 (1977).
- (9a) K. T. Potts, J. Baum and E. Houghton, *J. Org. Chem.*, **41**, 818 (1976); (b) H. Matsukubo and H. Kato, *J. Chem. Soc., Perkin Trans. I*, 632 (1975); (c) Th. Eicher and V. Schafer, *Tetrahedron*, **30**, 4025 (1974).
- (10) H. Matsukubo, M. Kojima and H. Kato, *Chem. Letters*, 1153 (1975).
- (11) H.-D. Martin and M. Hekman, *Angew. Chem., Int. Ed. Eng.*, **11**, 926 (1972).
- (12) D. Bellus, K. von Bredow, H. Sauter and C. D. Weis, *Helv. Chim. Acta*, **56**, 3004 (1973).
- (13) H. T. Nagasawa, J. A. Elberling, P. S. Fraser and N. S. Mizuno, *J. Med. Chem.*, **14**, 501 (1971).
- (14) A method involving iminium salt cyclizations has been published recently: I. G. Csendes, Y. Y. Lee, H. C. Padgett and H. Rapoport, *J. Org. Chem.*, **44**, 4173 (1979). However, these workers were unable to prepare the 1-azabicyclo[5.5.0]alkane system by this method.